REMARKS

The applicant acknowledges the withdrawal of the new matter rejection of claim 14 under 35 U.S.C. 112, the rejections of claims 14 and 16 under 35 U.S.C. 112, second paragraph, and the rejection of claims 14 and 16 under 35 U.S.C. 102(b) as being anticipated by Takasu et al. (Endocrinology, 1996, 137(12): 5537-43).

Claims 14, 16, and 39-48 are pending in this application; all stand rejected. Claim 48 was rejected under 35 U.S.C. § 101. Claim 14, 39-42, 44, and 47 were variously rejected under 35 U.S.C. § 102. Claims 16, 43, and 45-46 were variously rejected under 35 U.S.C. § 103. Claims 39-48 were rejected under 35 U.S.C. § 112, first paragraph. Claims 39-48 were rejected under 35 U.S.C. § 112, second paragraph.

Independent claim 14 has been amended to indicate that the range of PTH fragments claimed begins with those where the first residue is at position 9 or later in the human intact PTH sequence, having SEQ ID NO:1 (PTH_{1-84}). This is supported by the specification as recognized for the prior amendment in which position 8 or later was selected as the starting point for the peptide sequences claimed. Thus the amendment adds no new matter.

Claim 39 is amended to state that the treated subject is one "diagnosed with excessive PTH activity." Applicants believe this was inherent in the original claim, and making it explicit therefore adds no new matter.

Claim 39 is further amended by replacing the term 'anabolic' with the term 'catabolic'. This corrects an inadvertent error pointed out by the Examiner, thus it adds no new matter.

Claim 47 is amended to recite "a further effect" rather than "the further effect", to resolve an antecedent basis issue. It is further amended for clarity: the phrase "the PTH antagonist has a further effect" is repeated to clarify the meaning of the claim, as is the term "a subject". Each change merely emphasizes the original meaning, thus the amendment adds no new matter.

Claim 48 s amended to recite "a further effect" rather than "the further effect", to resolve an antecedent basis issue.

The foregoing amendments add no new matter, and entry of the amendments is respectfully requested.

The amendments are made solely to promote prosecution without prejudice or disclaimer of any previously claimed subject matter. With respect to all amendments and cancelled claims, Applicant has not dedicated or abandoned any unclaimed subject matter and moreover has not acquiesced to any rejections and/or objections made by the Patent Office. Applicant expressly reserves the right to pursue prosecution of any presently excluded subject matter or claim embodiments in one or more future continuation and/or divisional application(s).

Priority claim

The present specification was amended in the July 2, 1004 Amendment to claim benefit of provisional U.S. Patent Application No. 60/224,447, filed on August 10, 2000 under 35 U.S. C. 119(e). Also enclosed herewith a new Declaration and Power of Attorney that specifically claims priority to the provisional U.S. Patent Application No. 60/224,447. Applicant respectfully requests the acknowledgment of this priority claim.

Rejection under 35 U.S.C. § 101

Claim 48 was rejected under 35 U.S.C. §101 because the disclosed invention is allegedly inoperative, and therefore lacks utility. The Examiner based this rejection on Divieti, et al. (Endocrinology, 2002, 143(1): 171-176), saying that Divieti "discloses that human PTH-(7-84) acts via receptors distinct from the PTHIR (the abstract). As such, the present PTH antagonist, which is the same as that of Divieti's, would not be able to block a PTH binding site on the PTHR as it would not bind PTHR." Applicants respectfully traverse this rejection.

While the Divieti reference, dated January 2002, is not prior art to the present application, the applicant recognizes that it may be informative of the technical feasibility or

operability of the claims. Divieti teaches that the observed activity results from activity on "receptors distinct from the PTH1R and presumably specific for PTH C-fragments...", but this does not demonstrate that even PTH_{7-84}, let alone other truncated PTH peptides, fails to bind to all PTH receptors; at most, it shows that the observed biological activity (bone antiresorption) in a particular assay was not caused by binding specifically to PTH1R. It does not demonstrate that binding to PTH1R fails to occur at some biologically relevant concentration. Furthermore, the reference used human PTH fragments in a murine bioassay system.

In addition, it is generally known that the PTH receptor binding region in PTH falls within a region towards the C-terminus of PTH (1-38). For example, Gardella *et al.* teach that residues 24, 28 and 31 contribute to the PTH receptor interaction. (Gardella *et al.*, *Endocrinology* 132:2024-30 (1993), attached hereto as Exhibit A). Pellegrini *et al.* also teach that residues of the principal PTH receptor binding domain include residues 30 and 32. (Pellegrini *et al.*, *Biochemistry* 37:12737-43 (1998) 37), attached hereto as Exhibit B). Similarly, Barbier *et al.* suggest that residues 25-31 may bind to the PTH receptor. (Barbier *et al.*, *Biochemistry* 39:14522-30 (2000), attached hereto as Exhibit C). Accordingly, the PTH antagonists used in claim 48, *i.e.*, PTH_{2-84} to PTH_{34-84}, contain the sequences for binding to PTH1R receptor and would be able to block a PTH binding site on the PTH1R receptor.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 101.

Rejection under 35 U.S.C. § 112, first paragraph

Claims 39-48 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Examiner asserts that the claimed method for reducing an anabolic effect of PTH is inconsistent with the teachings of the specification, and suggests that the truncated PTH peptides of the invention would need to reduce a catabolic effect instead in order to treat hyperparathyroidism, osteodystrophy, osteoporosis, and hypercalcemia.

Applicant appreciates the Examiner's point, and have amended the claims to correct the erroneous description previously used. The amended claims are drawn to methods to reduce a *catabolic* effect of PTH on bone, which, as the Examiner points out, is both the expected effect of a PTH antagonist and an appropriate response to conditions characterized by excessive PTH activity. Since the error and the correction of the error would both have been obvious to one of ordinary skill from reading the specification, the correction does not add new matter if the prior claim was not new matter. See MPEP § 2163.07: an amendment to correct an obvious error does not constitute new matter where one skilled in the art would not only recognize the existence of the error in the specification, but also the appropriate correction. In re Oda, 443 F.2d 1200, 170 USPQ 268 (CCPA 1971). See also MPEP § 2163, summarizing In re Kóller: original claims comprise part of the patent's description of the invention. The applicant believes that the amended claim is now enabled by the specification and the ordinary skill in the art, and respectfully request withdrawal of this rejection.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 112, second paragraph

The Examiner also rejected claim 39 under 35 U.S.C. § 112 as being indefinite, for failing to identify what subject or condition warrants application of the claimed method. Claim 39 is now amended to recite that the subject is one "diagnosed with excess PTH activity". This limits the method claim to cover only applications of the pharmaceutical compositions to subjects expected to benefit from the claimed biological activity; such limitation would be inherent in the method as read by one of ordinary skill. Withdrawal of this rejection in light of the claim amendment is thus requested.

Claims 47 and 48 were rejected as indefinite for references to "the further effect", which term lacked antecedent basis. Each has been amended to recite "a further effect"; thus withdrawal of this rejection is requested.

Claims 40-46 were rejected under this section for depending from rejected claims; thus withdrawal of those rejections is requested once rejections to the independent claims are removed.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph.

Rejections under 35 U.S.C. § 102

Born

Claim 14 was rejected under 35 U.S.C. § 102(b) as being anticipated by Born, et al. (Endocrinology, 1988, 123(4): 1848-53). Applicant respectfully traverses this rejection.

Born discloses certain activities, or the lack thereof, for PTH_{3-84} and PTH_{8-84}. Neither of these species is within the amended claims. Nevertheless, the applicant points out that Born mostly demonstrates that PTH_{8-84}, the truncated PTH peptide closest to the present claims, was nearly inactive in their assays for PTH inhibitory activity: it had 1% of the activity of a synthetic bovine analog used as a standard, while PTH_{3-84} had 100x more activity than the same standard. (Born abstract.) While the Examiner notes that Born does not *explicitly* describe a pharmaceutical composition, the applicant points out that the extremely weak activity of PTH_{8-84} in the specific assay system used in Born would not motivate one to prepare a pharmaceutical composition. Thus Born does not anticipate the invention claimed, because it does not disclose a pharmaceutical composition, and it does not render the claimed invention obvious because it appears to show that the activity described all but disappears when truncating as many as 7 residues from the N-terminus of PTH. It thus teaches away from a genus of further-truncated PTH peptides, such as that presently claimed.

To advance prosecution and without acquiescence to the rejection, claim 14 has been amended to recite a PTH antagonist starting at any position spanning from position 9 through position 34 of SEQ ID NO:1 (PTH_{1-84}). Applicant respectfully submits that this amendment renders moot the anticipation rejection based on Born.

Fukuda

Claims 39-42, 44, and 47 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Fukuda, EP 0 528 271 A1. Applicant respectfully traverses this rejection.

The Examiner asserts that Fukuda teaches most of the limitations of the rejected claims, except for a pharmaceutical composition and asserts that "[a]lthough Fukuda does not specifically mention the treatment of hyperparathyroidism with said hPTH antagonist, Fukuda's 'the like' would inherently include hyperparathyroidism because it is well established that hyperparathyroidism is due to excess PTH..." Applicant respectfully disagrees.

First, claim 39 requires the use of a PTH antagonist that reduces the catabolic effect of PTH. Therefore, the PTH antagonist must counter the effect of PTH. Fukuda does not, explicitly or inherently, disclose the use of a PTH antagonist that counters the effect of PTH. Fukuda discloses "antagonists in which several amino acid residues on the N-terminal side of human PTH containing the C-terminal peptide chain are deleted, and peptides obtained by further subjecting the antagonists to the amino acid substitution mentioned above." (Fukuda at page 3, lines 12-14.) Fukuda also discloses "a human parathyroid hormone mutein comprising at least one modification which is selected from the group consisting of (i) deletion of 3 to 6 amino acid residues on the N-terminal side in the amino acid sequence of human parathyroid hormones, (ii) substitution of another lipophilic amino acid residue for at least one methionine residue in said amino acid sequence, and (iii) substitution of a cysteine residue for one amino acid residue within the region of amino acid residue Nos. 34 to 47." (Fukuda at page 3, lines 16-21.) Therefore, Fukuda does not teach whether the antagonizing effect of its mutants are from the N-terminal deletion or from other modifications of PTH sequence. Nor does Fukuda clarify the meaning of PTH antagonist, *i.e.*, whether the PTH antagonist counters the effect of PTH or it is simply less active then PTH.

In addition, Fukuda discloses that its PTH mutants can be agonists or antagonists. Fukuda states:

> The resulting human PTH mutein of the present invention are useful as therapeutic drug. When the resulting human PTH mutein is an agonist derivative, it can be used as therapeutic agents for various diseases caused by the abnormality of calcium metabolism, for example, osteoporosis and hypoparathyroidism, and as therapeutic agents for hypertension. Further, the human PTH antagonist derivatives can be used as therapeutic agents for hypercalcemia and hyperparathyroidism.

(Fukuda at page 9, lines 16-20.) This passage, however, does not teach which mutant is an agonist and which mutant is an antagonist. In other places, Fukuda teaches that the N-terminal deletional mutants, *e.g.*, PTH_{7-84}, have agonist activity. For example, at page 23, lines 20-45, the only bioactivity tests in Fukuda showed that PTH_{7-84} ([Leu^8] human PTH]) is as active as human PTH in increasing cAMP production. In other words, this data showed that PTH_{7-84} as an agonist, instead of an antagonist. And nowhere is there any disclosure or teaching that PTH_{7-84} can be used to counter the effect of human PTH.

The Court in Continental Can Co. USA, v. Monsanto Co., 948 F.2d 1264; 20 U.S.P.Q.2d 1746 (Fed. Cir. 1991) stated:

> To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 322, 326 (CCPA 1981) (quoting *Hansgrig v. Kemmer*, 102 F.2d 212, 214, 40 U.S.P.Q. 665, 667 (CCPA 1939) provides:
>
> > Inherency, however, may not be established by probabilities or possibilities. The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient. [Citations omitted.] If, however, the disclosure is sufficient to show that the natural result flowing from the operation as taught would result in the performance of the questioned function, it seems to be well settled that the disclosure should be regarded as sufficient.

(*See* also MPEP § 2100-54.) In the present case, Fukuda actually teaches that PTH_{7-84} has the agonist activity. Fukuda does not teach that PTH_{7-84} can possibly, let alone necessarily, be used to counter the effect of human PTH.

Similarly, a description of biochemical or biological activity does not render a pharmaceutical composition 'necessarily present'; an argument might be made that it could be possible to make a pharmaceutical composition and to use it to treat hyperparathyroidism, but those limitations are not necessarily present in the teachings of Fukuda. Thus the reference is not anticipatory.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 102.

Rejection under 35 U.S.C. § 103

Takasu in view of Fukuda

Claim 16 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Takasu, et al. (Endocrinology, 1996, 137(12): 5537-43) and Fukuda, EP 0 528 271 A1. The Examiner asserts that "Takasu discloses a truncated hPTH mutein, which N-terminal residue starts at position 35, i.e., hPTH(35-84), and is an antagonist of hPTH as it significantly inhibited the [^{35}S] hPTH(1-84) binding. Fukuda discloses several hPTH muteins, which comprise deletion of 3 to 6 amino acid residues on the N-terminal side of the sequence of hPTH, and teaches that these muteins function as antagonists of hPTH (page 3, lines 12-13). Further, Fukuda teaches that these compounds have more desirable properties in clinical application (page 3, lines 11-15), such as in the treatment of hypercalcemia and the like (page 2, lines 8-9)." Thus the Examiner asserts that one of ordinary skill would have found it obvious to combine the teachings of the two references. The applicant respectfully traverses this rejection.

To establish an obviousness rejection, the Office must demonstrate that the references provide both the motivation to combine the teachings of the references and a reasonable expectation of success with the combination, and must also show that the references provide all of the limitations of the claimed invention.

Claim 16 is directed to a PTH antagonist from PTH_{28-84} to PTH_{34-84}. Takasu teaches PTH_{35-84}. Fukuda, at most, teaches the deletion of 3-6 residues from the N-terminus of PTH. Takasu and Fukuda, whether individually or in combination, do not teach or suggest a PTH antagonist from PTH_{28-84} to PTH_{34-84}.

Fukuda

Claim 43 was rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fukuda, EP 0 528 271 A1, as applied to claims 14, 16, and 43. Applicant has addressed the rejection of claims over Fukuda above; the rejection of dependent claim 43 must be withdrawn if the independent claim from which it depends is allowable. Thus applicant requests the withdrawal of this rejection.

Fukuda in view of Kanmera

Claims 45 and 46 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Fukuda, EP 0 528 271 A1, as applied to claims 14, 16, and 43, and further in view of Kanmera et al., EP 0 451 867. Applicant respectfully traverses this rejection.

As discussed above, Fukuda does not teaches or suggest the use of a PTH antagonist that counters the effect PTH. Kanmera does not cure the defects of Fukuda. The PTH antagonist used in claims 45 and 46 end at position 84 of PTH. Kanmera simply does not teach or such any PTH antagonist that ends at position 84 of PTH. For example, Kanmera states that "[i]t is known that PTH fragments which lack several amino acids at the amino terminal and carboxy terminal of PTH, such as PTH (3-34), PTH (7-34) or their derivatives inhibit the PTH action, and they are useful as PTH antagonists." (Kanmera at page 2, lines 10-12.) The real PTH antagonists taught in Kanmera are derived from PTHrP. Kanmera states:

> As the result of extensive study for the purpose of obtaining PTHrP derivatives showing more potent PTH antagonistic activity than known PTH or PTHrP derivatives, such as [Tyr^{34}]-hPTH (3-34)-NH2, hPTHrP (3-34)-NH2 and [Leu^{11},D-Trp^{12}]-hPTHrP(7-34)-NH2,

> the present inventors have found that a certain class of PTHrP derivatives possess excellent antagonistic activity against PTH.

(Kanmera at page 2, lines 18-21.) Since PTH and PTHrP are two different proteins, neither Fukuda nor Kanmera teaches or suggests the PTH antagonist used in claims 45 and 46.

In view of the foregoing, Applicant respectfully requests reconsideration and withdrawal of the rejection under 35 U.S.C. § 103.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw all outstanding rejections of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no. 53221-2000300. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

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Respectfully submitted,

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